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16. Abstract (Limit: 200 words)

This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred:

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors
Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

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Office of Pesticide Programs (TS-766C)
Washington, DC 20460

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EPA Pesticide Fact Sheet

Name of Chemical: OXYTETRACYCLINE
Reason for Issuance: REGISTRATION STANDARD
Date Issued: DECEMBER 1988
Fact Sheet Number: 199

1. DESCRIPTION OF CHEMICAL

Generic Name: Oxytetracycline
Oxytetracycline calcium complex
Oxytetracycline hydrochloride

Chemical Name: 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydro-6-methyl-1,11-dioxo-2-naphthacenecarboxamide and its calcium complex and hydrochloride salts.

Trade Names: Glomycin, Terrafungine, Riomitsin, Hydroxy-tetracycline, Berkmycin, Biostat, Impercin, Oxacycline, Oxyatets, Mycoshield, Agricultural Terramycin, Terramycin Hydrochloride, Terramycin.

Chemical Class: Antibiotic (produced by the actinomycete Streptomyces rimosus)

Pesticide Type: Plant Fungicide/Bactericide and Algicide

CAS Registry Number: 79-57-2 (oxytetracycline)
7179-50-2 (calcium complex)
2058-46-0 (hydrochloride)

EPA Shaughnessy Codes: 006304 (oxytetracycline)
006321 (calcium complex)
006308 (hydrochloride)

Empirical Formulae: $C_{22}H_{24}N_2O_9$ (oxytetracycline) Mol. Wt. 460.44
$C_{22}H_{22}N_2O_9$ Ca (calcium complex) M.W. 498.52
$C_{22}H_{24}N_2O_9$ HCL (hydrochloride) M.W. 496.9

Year of Initial Registration: August 1974

U.S. and Foreign Producers: Pfizer, Inc.

2. USE PATTERNS AND FORMULATIONS

Type of Pesticide: Plant Fungicide/Bactericide and Algicide.

Pests Controlled: Bacterial and fungal diseases and slime-forming microorganisms.

Registered Uses:

1. Calcium oxytetracycline [17% WP]:
Nectarines, peaches, pears, and creeping Bentgrasses.

2. Oxytetracycline hydrochloride [21.6% Soluble Concentrate.
-(Tree Trunk Injection) pears, peaches, and ornamental palms)
- Marine antifoulant paint additive.

3. Oxytetracycline hydrochloride [21.6% Soluble Concentrate.
Formulation Intermediate for Marine antifoulant additive.

Predominant Uses: Pears and peaches (98%).

Minor Uses: Ornamental palms and Bentgrasses.

Annual Usage: 21,350 pounds/ai

Method of Application: Foliar, tree injection, and brush on (marine use).

3. SCIENCE FINDINGS

Summary Science Statement

1. Oxytetracycline hydrochloride oncogenicity data indicates equivocal evidence of oncogenicity in male and female rats. The Agency concludes that, although the findings were termed "equivocal" by the National Toxicology Program, they do not represent positive evidence of carcinogenicity in the rat. A similar study in mice indicated no evidence of oncogenicity.

2. Tolerances for oxytetracycline are limited to peaches (which includes nectarines) and pears, 0.1 ppm and 0.35 ppm respectively. A Reference Dose (RfD) of 1.0 mg/kg/day has been established based on several chronic studies. The Theoretical Maximum Residue Contribution (TMRC) for the U.S. population is 0.000065 mg/kg/day, corresponding to 0.006% of the RfD. A proposed increase in the peach tolerance from 0.1 to 0.35 ppm would result in a TMRC of 0.000118

mg/kg/day. The largest subgroups, nursing and non-nursing infants, represent 0.061% and 0.076% respectively of the current RfD.

3. The potential for development of oxytetracycline resistance due to increased background levels from pesticidal uses to applicators and field workers appears minimal.

4. The Agency is unable to assess the potential for oxytetracycline to contaminate ground water because the environmental fate of oxytetracycline is uncharacterized.

5. The Agency is unable to assess the ecological effects of oxytetracycline on terrestrial or aquatic wildlife, because no data are available.

Toxicology Characteristics

Oxytetracycline has been used extensively for over 37 years in animals and in man. It is one of a group of broad spectrum antibiotics known as tetracyclines which were developed for control of bacterial diseases in man and animals. As a result of its human drug use, there is an extensive body of toxicological data available on oxytetracycline. Thus, all toxicological data requirements have been waived.

Chronic toxicity

Due to various deficiencies, the available studies do not fulfill current requirements. Additional data are not required, based upon availability of both animal and human data from oxytetracycline's drug uses.

Two 2-year chronic toxicity studies in rats are available. In one study, Osborne-Mendel rats were fed diets containing 0, 100, 1000 and 3000 ppm, oxytetracycline hydrochloride in the diet for 24 months. The NOEL was determined to be 3000 ppm, approximately 150 mg/kg/body weight/day, highest dose tested.

In a second study, Sprague Dawley rats were fed diets containing 0,100, and 1000 ppm oxytetracycline hydrochloride in the diet for 24 months. The NOEL for oxytetracycline hydrochloride was 1000 ppm, 50 mg/kg/day, highest dose tested.

Two chronic toxicity studies in dogs are available. In the first study, dogs were fed diets containing 0, 100, 3000, and 10000 ppm of oxytetracycline hydrochloride in the diet for 24 months. A yellow discoloration of the long bones and brownish discoloration of the thyroid was observed in all dosed animals at necropsy. The NOEL was determined to be 10000 ppm, approximately 250 mg/kg/day, highest dose tested.

In a second study, mongrel dogs were fed diets containing 0, 5000, and 10000 of oxytetracycline hydrochloride in the diet for 12 months. The NOEL was determined to be 10000 ppm, approximately 250 mg/kg/day, highest dose tested.

Oncogenicity

NCI/NTP Oxytetracycline Oncogenicity Study in the F344N/Rat

In this study, oxytetracycline hydrochloride (purity 98.8%) was administered to groups of F344/N rats fed 0, 25000, and 50000 ppm in the diet for 103 weeks. Fatty metamorphosis of the liver was increased in rats in the low dose group. The National Toxicology Program concluded that ". . . . there was equivocal evidence[1] of carcinogenicity for male F344/N rats as indicated by increased incidences of pheochromocytomas of the adrenal gland. There was equivocal evidence of carcinogenicity for female F344/N rats as indicated by increased incidences of adenomas of the pituitary gland in the high dose group."

NCI/NTP Oxytetracycline Oncogenicity Study in the B6C3F1 Mouse

In this study, oxytetracycline hydrochloride (purity 98.8%) was administered to groups of B6C3F1 mice fed 0, 6300, and 12500 ppm in the diet for 103 weeks. The National Toxicology Program concluded that "... there was no evidence of carcinogenicity for male or female B6C3F1 mice fed diets containing 6300 or 12500 ppm of oxytetracycline hydrochloride for 2 years."

Teratogenicity

Female Charles River CD rats were dosed during days 6 through 15 of gestation with 1200, 1350, or 1500 mg/kg of oxytetracycline hydrochloride. There were dose-related decreases in maternal survival and body weight gain, and increases in the incidence of respiratory difficulties and rough coat. In addition, there were significant dose-related decreases in the percent of treated dams found pregnant. There was also a dose-related decrease in fetal body weight. The high incidence of maternal deaths and the fetotoxicity noted in all dose levels tested did not allow for an establishment of a NOEL. The LEL was 1200 mg/kg/day (lowest dose tested).

The significant findings discussed in this study can be attributed to the excessive dose levels used, and the overly stressing of the treated dams.

Female CD-1 mice were dosed during day 6 through 15 of gestation with 0, 1325, 1670, and 2100 mg/kg oxytetracycline hydrochloride. No adverse effects were demonstrated, due probably to the low dose levels used. The NOEL for maternal and developmental toxicity in this study was 2100 mg/kg (highest dose tested).

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[1] The NCI/NTP uses five levels of interpretative evaluations in animal carcinogenesis studies; in decreasing order of strength (not potency or mechanism) of the experimental evidence, these are: (i) clear evidence ofcarcinogenicity (ii) some evidence of carcinogenicity, (iii) equivocal evidence of carcinogenicity, (iv) no evidence of carcinogenicity, and (v) inadequate study of carcinogenicity.

Antibiotic Microbial Resistance

Mature beagles were fed a diet containing 0, 2, or 10 ppm, approximately of oxytetracycline for 44 days. The 10 ppm (0.25 mg/kg/day) diet resulted in a shift from a predominantly drug-susceptible population of enteric lactose-fermenting organisms to a multiple antibiotic-resistant population. A shift to drug-resistance did not occur in the group fed 2 ppm approximately 0.05 mg/kg/day. The NOEL was 0.05 mg/kg/day.

4. TOLERANCE ASSESSMENT

Tolerances have been established for residues of oxytetracycline in two raw agricultural commodities (40 CFR 180.337). Use of oxytetracycline as a drug in food animals is regulated by the FDA according to 21 CFR 520, 522, 524, and 558. The FDA has established tolerances for oxytetracycline in or on meat, fat, meat byproducts, and in uncooked edible tissues of salmonoid fish and catfish (21 CFR 556.500).

No data are available to evaluate the nature of the residue of oxytetracycline in plants. The Agency has assessed the need for data reflecting the metabolism of oxytetracycline in plants and has concluded that these data are not required because of the drug uses of oxytetracycline.

No data are available to evaluate the nature of the residue of oxytetracycline in animals. However, data on the metabolism of oxytetracycline in food animals are not required: residues of oxytetracycline in meat and milk are unlikely since there are no registered uses of animal feed items at the present time.

The available microbiological assay method for the determination of oxytetracycline residues in or on peaches, nectarines and pears is adequate for data collection and for tolerance enforcement. The Agency will not require any additional analytical methods at this time. The method is similar to Final Action Microbiological Methods I and II in the AOAC Official Methods of Analysis (1984;42.293-42.298).

5. Summary of Regulatory Positions

Oxytetracycline is not a candidate for Special Review at this time.

Oxytetracycline does not meet the criteria for restricted use classification.

The Agency will continue to grant new uses for oxytetracycline.

The Agency will propose that the tolerance level for peaches be increased from 0.1 ppm to 0.35 ppm.

The Agency will not propose the establishment of crop group tolerances for pome fruits or stone fruits.

Current tolerances are sufficient to cover the actual residues resulting from tree injections (pears only) and foliar applications.

The Agency is deferring its decision concerning the potential of oxytetracycline to contaminate groundwater until information on its environmental fate has been submitted and evaluated.

The Agency believes that the potential for development of resistant microorganisms in applicators and/or field workers as a result of exposure are negligible.

Potential for development of oxytetracycline resistant microorganisms as a result of dietary exposure is minimal.

6. Summary of Major Data Gaps

Environmental fate/Exposure:[2]	Timeframe for Submission
Hydrolysis	9 Months
Photodegradation in water and in soil	9 Months
Metabolism Studies (lab)	
-Aerobic Soil	27 Months
-Anaerobic Soil	27 Months
-Anaerobic Aquatic	27 Months
-Aerobic Aquatic	27 Months
Leaching and Adsorption/Desorption	12 Months
Dissipation Studies (field)	
-Soil	27 Months
-Aquatic (Sediment)	27 Months
Accumulation in Fish	12 Months
Fish & Wildlife:	
Avian Acute Oral LD50	9 Months
Avian Dietary LC50	9 Months
Freshwater Fish LC50 (TGAI)[3]	9 Months
Freshwater Invertebrate (TGAI)	9 Months
Product Chemistry	
All product chemistry studies	9 Months

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[2] Environmental Fate data requirements only for calcium oxytetracycline.

[3] TGAI: Technical grade of the active ingredient

7. CONTACT PERSON AT EPA

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DISCLAIMER: The information in this Pesticide Fact Sheet is a summary only and is not to be used to satisfy data requirements for pesticide registration and reregistration. The complete Registration Standard for the pesticide may be obtained from the National Technical Information Service. Contact the Product Manager listed above for further information.